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Glutamatergic antipsychotic drugs - a new dawn in the treatment of schizophrenia?

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Abstract

Growing evidence for glutamate abnormalities in schizophrenia support the development of novel antipsychotic agents targeting this system. Early studies investigating modulation of the glutamate system using glycine, D-serine and sarcosine in patients with schizophrenia have demonstrated significant effects, particularly on negative symptoms, conventionally thought to be refractory to antipsychotic drug treatment. Drugs targeting the glutamate system also have a completely different side-effect profile to dopamine D2 antagonists, with no propensity to extrapyramidal side-effects, prolactinaemia or weight gain. It has been hypothesised that glutamatergic drugs may be of benefit to the 20-30% of individuals with schizophrenia who fail to show any response to dopaminergic agents, and may be particularly useful in the early stages of the illness, where they may be disease-modifying. A number of glutamatergic compounds have been reported as having promising results in phase 2 drug trials. If these reach the clinic, they will represent the first truly novel approach to pharmacotherapy in schizophrenia for more than 50 years.

Introduction

For more than 50 years, the only effective antipsychotic drugs available have been dopamine D2 receptor antagonists {{948 Kapur,S. 2003;}}, with their clinical potency directly corresponding to their affinity at D2 receptors {{137 Seeman,P. 1975;}}. Despite leading to at least a partial clinical response in around 2/3 patients with schizophrenia, 1/3 patients will fail to respond to D2 antagonists {{818 Stone,J.M. 2010;}}. Furthermore, although positive symptoms generally show a reasonable response to these drugs, there frequently remain a core of negative symptoms that are refractory to antipsychotic treatment {{230 Buchanan,R.W. 1998;232 Tamminga,C.A. 1998;231 Javitt,D.C. 2001;}}.

All currently available antipsychotic drugs have significant, and sometimes potentially life-threatening, side-effects, which may lead to discontinuation of the treatment. Although the second generation of antipsychotic drugs have a lower incidence of extrapyramidal side effects, they are associated with other debilitating effects such as impaired glucose tolerance and weight gain, which can have significant health consequences. Thus, there has been a great deal of interest in developing new targets for pharmacological treatment in schizophrenia – drugs which might have fewer side effects and/or lead to response in patients who do not respond fully to currently available drugs {{818 Stone,J.M. 2010;}}. So far, the only major advance in drug treatments for schizophrenia has been the discovery of clozapine, which has been consistently shown to have superior efficacy in patients unresponsive to other antipsychotic drugs {{139 Kane,J. 1988; 930 McEvoy,J.P. 2006;}}. No other agent developed since clozapine has shown equivalent efficacy, and improvements over first generation antipsychotic drugs have been incremental at best. Part of the reason for this lack of rapid progress may be due to the fact that drug development in schizophrenia has primarily focused on the strategy of developing new drugs that act on the dopamine system rather than developing compounds for other targets.

Glutamatergic neurotransmission

Glutamate is the main excitatory neurotransmitter in the brain. Between 60 and 80 percent of total brain metabolic activity in the non-stimulated cerebral cortex is utilised by glutamatergic neurones, with the remainder being used by GABAergic neurones and glial cells. The synaptic release of glutamate and recycling to glutamine in astrocytes is a major metabolic pathway (figure 1), and accounts for between 80 and 100 percent of total glutamate trafficking, and it is now accepted that no meaningful distinction can be made between metabolic and neurotransmitter glutamate {{370 Rothman,D.L. 2003;}}.

Glutamate acts at two main subtypes of neuroreceptor, the metabotropic glutamate receptors and the ionotropic glutamate receptors. Metabotropic glutamate receptors (mGluR) are composed of three groups (group I-III) distinguished by their sequence homology, pharmacology and second messenger systems. Group I receptors (mGluR1 and mGluR5) are predominantly postsynaptic in somatodendritic domains and couple via G_q/G_{11} to phospholipase C, whereas group II (mGluR2 and mGluR3) and III (mGluR4, mGluR6, mGluR7 and mGluR8) are coupled via G_i/G_o to inhibition of adenylate cyclase activity and are primarily presynaptic in axonal domains and terminals, where they modulate neurotransmitter release {{886 Kew,J.N. 2005;}}.

Ionotropic glutamate receptors are also divided into three groups, named after the agonists originally found to selectively activate them: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) receptors. The ionotropic glutamate receptors are all heteromeric ion channels, composed of multiple protein subunits. When activated they lead to an increase in cation conductance with differential permeability to Na^+ and Ca^{2+} depending upon

receptor type and subunit composition. NMDA receptors in the adult brain generally show increased Ca^{2+} conductance on activation, whereas kainate receptors lead to an increase in Na^+ conductance. AMPA receptors expressed on GABAergic hippocampal and amygdala interneurons appear to lack an edited GluR2 subunit, and show preferential Ca^{2+} conductance, whereas those on pyramidal neurons are non- Ca^{2+} permeable {{886 Kew,J.N. 2005;415 Dingledine,R. 1999;}}.

NMDA receptor structure and function

The NMDA receptor is a heteromeric ion channel, formed from a number of subunits (NR1, NR2A-D, NR3A-B). NR1 and NR2(A-D) subunits are obligatory for a functional NMDA receptor, and contain binding sites for glycine (glycine_B site) and glutamate respectively. NR2 subunits show distinct regional and developmental distribution, with NR2A and NR2B being expressed primarily in the forebrain, NR2C in cerebellar granule cells and NR2D being expressed during foetal development in the midbrain and diencephalon. NR3 subunits require both NR1 and NR2 subunits to form functional NMDA receptors. NR3A receptors are expressed primarily during development, and NR3B are only found in somatic neurons in brainstem and spinal cord. Activation of the NMDA receptor requires two obligatory co-agonists, binding at the glycine and glutamate sites. Two independent glycine, and two independent glutamate binding sites appear to be required. Therefore, it has been suggested, the minimum requirement for a functional NMDA receptor is two NR1 and two NR2(A-D) subunits {{886 Kew,J.N. 2005;}}. At resting potential, NMDA receptors are blocked by extracellular Mg^{2+} , which binds to an intrachannel site of the NMDA receptor complex. In order to allow Ca^{2+} to enter the cell, in addition to glutamate and glycine binding, the cell must depolarise, removing the Mg^{2+} block {{415 Dingledine,R. 1999;}} (see figure 2). Uncompetitive allosteric antagonists of the NMDA receptor such as ketamine, phencyclidine (PCP) and dizoiline (MK-801) bind to the inside of the NMDA receptor ion channel when it is in its open state, and prevent Ca^{2+} influx.

Glutamate and schizophrenia

There is growing evidence that changes in glutamatergic neurotransmission may occur in schizophrenia, and it has been hypothesized that glutamatergic changes may precede, or give rise to, alterations in other downstream neurotransmitter systems such as dopamine {{317 Stone,J.M. 2007;}}. The glutamate hypothesis of schizophrenia was founded on a number of observations. Drugs that act as uncompetitive antagonists at NMDA receptors such as phencyclidine (PCP) and ketamine reliably and instantly induce a drug-induced state that closely resembles the symptoms of schizophrenia, including thought disorder, odd ideas and delusions , cognitive impairment, and, most notably, an emotional withdrawal that has been likened to the negative symptoms of schizophrenia {{142 Krystal,J.H. 1994; 820 Morgan,C.J. 2006; 687 Javitt,D.C. 2007;}}. In contrast, drugs that increase brain dopamine transmission, such as amphetamine, do not induce cognitive or negative symptoms {{158 Krystal,J.H. 2005;}}. Blockade of NMDA receptors by ketamine has been shown to be most closely related to negative, rather than positive symptoms {{372 Stone,J.M. 2008;}}, suggesting that dopamine and glutamatergic changes may give rise to different symptoms of the illness {{158 Krystal,J.H. 2005; 372 Stone,J.M. 2008;}}. Secondly, candidate risk genes for schizophrenia are not related to the dopamine system, but rather converge on molecules involved in glutamatergic neurotransmission {{118 Harrison,P.J. 2005;}}.

These findings suggest, as previously hypothesised, that negative and cognitive symptoms may be at the core of schizophrenia {{204 Andreasen,N.C. 1999;}}. Cognitive symptoms have been found to be closely associated with negative symptoms in patients with schizophrenia {{932 Addington,J. 1991;931 Ventura,J. 2009;}}, and negative symptoms are most closely associated with functional outcome {{931 Ventura,J. 2009;}}. Early and subtle cognitive decline is one of the first (usually

undetected) symptoms of schizophrenia {{175 Bilder,R.M. 2006;}}, and it is interesting to speculate that these changes might arise secondary to abnormalities in NMDA receptor function or glutamatergic transmission.

Studies of the effect of NMDA receptor antagonists on brain structure and function are supportive of the hypothesis of abnormalities of glutamatergic transmission in schizophrenia. Seminal work by Olney and Farber showed that exposure of rats to systemic injections of NMDA receptor antagonists led to neurotoxic changes in cortical brain regions, which they suggested closely resembled the reductions in grey matter volume seen in patients with schizophrenia {{78 Olney,J.W. 1995;}}. They showed that antagonists for the AMPA subtype of glutamate receptor blocked this toxicity, and hypothesised that the cortical toxicity was caused, somewhat counter-intuitively, by excess cortical glutamate release. They put forward the theory that NMDA receptors expressed on GABAergic interneurons were particularly sensitive to NMDA receptor antagonists and that the resultant reduction in inhibitory tone led to disinhibition of glutamatergic projection neurons leading to glutamate release and excitotoxicity {{78 Olney,J.W. 1995;}} (figure 3).

This hypothesis was supported by later microdialysis studies showing increased glutamate in prefrontal cortex following systemic administration of ketamine {{98 Moghaddam,B. 1997;107 Lorrain,D.S. 2003;}}. Interestingly, injection of the NMDA receptor antagonist MK-801 into cortical regions did not lead to any evidence of neurodegenerative changes, whereas injection into anterior thalamus led to the same cortical changes as seen with systemic administration {{174 Sharp,F.R. 2001;}}, suggesting that thalamus might be a primary site of NMDA receptor blockade in the generation of downstream effects by NMDA receptor antagonists, and, by extension, may also be a site of NMDA receptor dysfunction in schizophrenia {{77 Olney,J.W. 1999;317 Stone,J.M. 2007;}}.

Studies of patients with schizophrenia and first episode psychosis, and in individuals with prodromal symptoms of schizophrenia (“at risk mental state” - ARMS), who are at high risk of developing schizophrenia {{322 Phillips,L.J. 2000;}}, have generally been supportive of the hypothesis of NMDA receptor dysfunction and altered glutamate transmission in the illness {{821 Stone,J.M. 2009;}}. A study using a single photon emission tomography (SPET) ligand for the NMDA receptor revealed that individuals with schizophrenia who were not currently medicated had lower NMDA receptor binding in the left hippocampus compared to healthy volunteers {{188 Pilowsky,L.S. 2006;}} (figure 4). This finding was in close agreement to an earlier post-mortem study of mRNA of the NMDA receptor subunit NMDAR1, which revealed that patients with schizophrenia showed reduced levels in left dentate gyrus {{116 Law,A.J. 2001;}}. Furthermore, in patients treated with typical antipsychotic drugs, levels of NMDA receptor binding in the left hippocampus were inversely correlated with negative symptoms {{188 Pilowsky,L.S. 2006;}}.

Studies employing Proton Magnetic Resonance Spectroscopy (1H-MRS) have measured cortical glutamate and glutamine levels in individuals at high risk of psychosis, as well as patients with first episode psychosis and chronic schizophrenia. Glutamine is produced in astrocytes following synaptic release of glutamate, and so has been suggested to be a marker of glutamatergic transmission. Studies in individuals at risk of psychosis, and patients with first-episode psychosis have found evidence of increased glutamatergic transmission in anterior cingulate and frontal cortex {{660 Stone,J.M. 2009;643 Théberge,Jean 2002;103 Tibbo,P. 2004;542 Bartha,Robert 1997;}}. In contrast, studies of patients with chronic schizophrenia have generally found normal or reduced cortical glutamate levels {{638 Tayoshi,ShinYa 2009;642 Théberge,Jean 2003;379 Ohrmann,P. 2005;601 Lutkenhoff,E.S. 2008;905 Rowland,L.M. 2009;906 Block,W. 2000;907 Kegeles,L.S. 2000;908 Ongur,D. 2009;}}.

Subcortical measures of glutamate are less consistent. Individuals at risk of psychosis have been shown to have reduced thalamic glutamate levels {{821 Stone,J.M. 2009;}}, whereas patients with first-episode and chronic schizophrenia have been reported to have increased thalamic glutamine {{642 Théberge,Jean 2003;643 Théberge,Jean 2002;}}. The reason for this discrepancy is not clear, but it may represent differences in imaging methodology, or possibly differences in illness subtype as increases in cortical glutamate release could be driven by reduced subcortical glutamatergic transmission on GABA interneurons or by dysfunctional NMDA receptors expressed on the same population of neurons{{78 Olney,J.W. 1995;}}.

There has been much speculation about how glutamate and dopamine may be related in schizophrenia, and whether glutamate or dopamine might be more “upstream” in the illness. Olney and Farber hypothesised that glutamatergic changes might be related to a primary dopaminergic abnormality {{78 Olney,J.W. 1995;}}, whereas others have suggested that abnormalities in glutamate transmission or NMDA receptor function could drive changes in dopamine {{822 Coyle,J.T. 2006;118 Harrison,P.J. 2005;317 Stone,J.M. 2007;}}. A plausible animal model of schizophrenia suggests that increased glutamate efferents from hippocampus may drive increased dopamine neuron responsivity {{690 Lodge,D.J. 2006;}}(figure 5). In support of this hypothesis, lower levels of hippocampal glutamate (potentially driving increased hippocampal outputs through reduced stimulation of GABA interneurons) are associated with increased striatal [18F]DOPA uptake (a marker of presynaptic dopamine function) in individuals with an ARMS but not in healthy volunteers {{798 Stone,J.M. 2010;}}. The fact that this relationship was found in individuals with an ARMS and not in healthy volunteers suggests GABA interneurons in ARMS subjects may be more sensitive to presynaptic glutamate levels – possibly due to lower hippocampal NMDA receptor expression {{188 Pilowsky,L.S.

2006;}} (figure 5). Drugs targeting glutamatergic transmission might help to normalise these deficits and have additional downstream effects on normalising dopamine neuron activity.

Drugs targeting glutamate abnormalities in schizophrenia – studies in patients

A number of different potential targets have been suggested to reverse the hypothesised abnormality of glutamatergic transmission in schizophrenia {{821 Stone,J.M. 2009;}} - see figure 6. These include enhancement of the function of NMDA receptors expressed on GABAergic interneurons – by increasing synaptic glycine levels, through direct action at the glycine_B site, or by mGlu5 receptor agonism; enhancement of GABAergic interneuron function (through agonism of Trk1 receptors, alpha-7 nicotinic receptors or M1 receptors); enhancement of GABA tone on glutamatergic projection neurons (through drugs with preferential effects at alpha-2 containing GABA receptors); and reduction of the effect of excess downstream glutamate release by antagonism of AMPA glutamate receptors, or by reducing glutamate release through agonism of mGlu2/3 autoreceptors (figure 6).

Enhancement of NMDA receptor function

Several studies have investigated the effect of drugs which increase NMDA receptor function via the NMDA receptor glycine site: either increasing synaptic glycine levels by inhibiting type 1 glycine transporters (GlyT1) and preventing reuptake of synaptic glycine (sarcosine), or by acting as agonists at the glycine_B modulatory site (glycine and D-serine). As these compounds were not developed as CNS agents, relatively high doses are required for a clinical response (30-60g glycine per day has commonly been used). Nonetheless, a number of studies have employed these agents as adjunctive treatments in patients with schizophrenia. These have recently been reviewed in a meta-analysis, which showed a modest effect on both positive and negative psychotic symptoms {{519 Tsai,G.E. 2009;}}. No trials of glycine_B agonists as monotherapy have been published to date, and it is possible

that the effect size would be more marked when used as first line treatment. A single study of sarcosine as monotherapy showed efficacy, but patients were randomised to low (1g) or high (2g) dose sarcosine and so a direct comparison against dopaminergic agents has not yet been made {{840 Lane,H.Y. 2008;}}. It is interesting to note that glycine, D-serine and sarcosine did not have any additional effect when added to clozapine {{519 Tsai,G.E. 2009;}}, possibly because part of the superior efficacy of clozapine may be due to intrinsic agonist action at the glycine_B modulatory site {{837 Schwieler,L. 2008;}}. It must be noted that other currently available antipsychotic drugs (including haloperidol, thioridazine, chlorpromazine and clozapine) appear to interact with GlyT1 as non-competitive antagonists at therapeutic doses.

Reduction of downstream glutamate release and its effects

Drugs enhancing the function of alpha-2 subunit containing GABA-A receptors should, theoretically lead to reduced downstream glutamate release (figure 6) {{227 Lewis,D.A. 2005;}}. One study of MK-0777, a benzodiazepine-like drug with selectivity as a partial agonist at alpha-2 and alpha-3 GABA-A receptor subunits reported improved cognition in patients with schizophrenia, but no effect on psychotic symptoms {{880 Lewis,D.A. 2008;}}.

Lamotrigine, a drug which inhibits glutamate release, has been investigated as an adjunctive treatment in schizophrenia. Lamotrigine has been shown to reverse positive, negative and cognitive symptoms associated with ketamine administration in healthy volunteers {{216 Hosak,L. 2002;}}, and to reverse ketamine-associated changes in brain function measured using fMRI {{665 Deakin,J.F. 2008;}}. A recent meta-analysis suggests that lamotrigine, in contrast to drugs acting through glycine enhancement of NMDA receptor function, is effective as an add-on medication for patients who are

only partially responsive to clozapine, although effects were relatively modest {{838 Tiihonen,J. 2009;}}.

Glutamate mGlu 2/3 receptors are presynaptic autoreceptors {{886 Kew,J.N. 2005;}}. Agonists inhibit synaptic glutamate release (figure 6), and have been shown to reduce the effects of NMDA receptor antagonists, and amphetamine in both animal and human studies {{384 Moghaddam,B. 2004;386 Javitt,D.C. 2004;}}. A recent phase 2 trial of an mGlu2/3 receptor agonist (LY2140023 – an oral prodrug of LY404039), in a sample of patients with chronic schizophrenia, reported significant improvement in positive and negative symptoms compared to placebo {{354 Patil,S.T. 2007;}}. Olanzapine (15 mg daily) was used as an active control group in this study, and although not planned, a post-hoc comparison of olanzapine vs. LY2140023 revealed no statistically significant difference in terms of response to positive and negative symptoms. LY2140023 showed no propensity to elevated prolactin, weight gain or extrapyramidal side-effects, however. It's main reported side effects were affective lability (although this was reported to be beneficial in some patients who had severe affective flattening leading to increased emotional response and spontaneous emotional fluctuations), and a mild reduction in body weight and body mass index. One curious feature of the study was that the group of patients on placebo showed no improvement during the trial duration – whereas it is usual for improvement in symptomatology to be seen in patients in clinical trials on both placebo and active drug. A subsequent phase II trial of LY2140023 was reported by Lilly to be “inconclusive” due to a large placebo response – with neither LY2140023 nor olanzapine showing a significant improvement over placebo. They also reported that convulsions occurred in 3 out of the 669 patients recruited {{933 Kinon, Bruce J. 2010;}}. The study has not been published in full, and it is not clear whether Lilly plan to pursue further trials using this prodrug.

It has been suggested that mGlu2/3 agonists may work primarily through dopaminergic mechanisms {{909 Seeman,P. 2009;}}. However, recent work reveals that the efficacy of mGlu2/3 agonists to block the effects of amphetamine, ketamine and PCP are lost in mGlu2/3 knockout mice {{888 Fell,M.J. 2009;}}. It is possible that mGlu2/3 agonists may have downstream effects reducing D2High expression {{887 Seeman,P. 2009;}}. Further studies of LY404039, LY2140023 and related compounds are awaited.

Topiramate, an antiepileptic drug with AMPA antagonist properties has been found to be effective as an adjunctive therapy in treatment-resistant patients with schizophrenia {{201 Tiihonen,J. 2005;}}, and to reduce the effects of MK-801 in rats {{203 Deutsch,S.I. 2002;}}, although it is possible that these effects of topiramate may occur through enhancement of GABA transmission, as AMPA antagonism only occurs at higher concentrations {{202 Gibbs, J. W.,3rd 2000;}}.

Other Mechanisms

The antibiotic minocycline has, somewhat unexpectedly, been shown to inhibit the effects of NMDA receptor antagonism by MK-801 on rats {{845 Levkovitz,Y. 2007; 846 Zhang,L. 2007;}}, and to reverse PCP-induced cognitive deficits {{847 Fujita,Y. 2008;}}. A double-blind randomised controlled trial of minocycline as add-on treatment in patients with early phase schizophrenia (within the first 5 years of diagnosis) revealed a significant effect on negative and cognitive symptoms {{848 Levkovitz,Y. 2010;}}. Although the exact mechanism of action for minocycline in schizophrenia has still to be ascertained, it is possible that its effect arises through the inhibition of glutamate excitotoxicity (mediated via nitric oxide) by blocking p38 MAP kinase and c-jun N-terminal kinase (mitogen-activated protein kinases responsive to stress stimuli that regulate cellular functions including

neurodegeneration, apoptosis, cell differentiation and proliferation) {{850 Wilkins,A. 2004; 849 Pi,R. 2004;}}.

Cannabidiol (CBD), a constituent of cannabis, may also have a modulatory effect on glutamatergic transmission, as it has been shown to inhibit ketamine and MK-801 induced effects in animal models {{853 Moreira,F.A. 2005; 877 Long,L.E. 2006;}}, and in humans {{839 Hallak,J.E. 2010;}}. Cannabis users with detectable levels of both CBD and delta-9 tetrahydrocannabinol (THC) in hair samples reported a lower incidence of schizophrenia-like symptoms than those in whom THC alone was detected {{879 Morgan,C.J. 2008;}}. Furthermore, acute intoxication with cannabis containing low CBD led to impairments in recall, whereas high CBD cannabis did not induce any cognitive deficits {{878 Morgan,C.J. 2010;}}. Cannabidiol has been shown to have the opposite effect to THC on neural activation measured using fMRI during an emotional processing task and a verbal memory task {{934 Bhattacharyya,S 2010; 935 Fusar-Poli,P. 2009;}}, and pre-treatment with cannabidiol significantly attenuates the psychotogenic effects of THC {{936 Karniol,I.G. 1974; 934 Bhattacharyya,S 2010;}}. Preliminary work suggests that CBD is effective as an antipsychotic in patients with schizophrenia {{291 Zuardi,A.W. 2006;}}, although it had no additional beneficial effect in a small open-label study of clozapine-resistant patients {{291 Zuardi,A.W. 2006;}}.

The mechanism of action of CBD has not yet been completely elucidated. It has been demonstrated that CBD antagonises the inhibitory effect of endocannabinoids and THC on GABA and glutamate transmission, mediated via CB1 receptors {{881 Godino Mdel,C. 2007; 882 Neu,A. 2007;}}. Given the hypothesised mechanism of ketamine action on GABA and glutamate systems, it is possible that the enhancement of GABA-A function is its primary mode of action in reducing ketamine-induced effects (figure 6). However, a CB1 antagonist was not found to be effective in patients with schizophrenia

{{883 Meltzer,H.Y. 2004;}}, and there is growing evidence that some of the beneficial effects of CBD, like minocycline, may be mediated via inhibition of p38 MAP kinase {{885 Esposito,G. 2006;884 El-Remessy,A.B. 2008;}}.

Drugs targeting glutamate in schizophrenia – drugs in development.

GlyT1 Inhibitors

Several pharmaceutical companies have published data on GlyT1 receptor inhibitors (see Table 1). Roche reported in a press release that their GlyT1 inhibitor, RG1678, was successful in treating negative symptoms in a phase-2 drug trial, but they have not published any further data on this compound at present {{889 Pinard,E. 2010;}}. Johnson and Johnson have reported that the GlyT1 inhibitor, R231857, improved scopolamine-induced cognitive impairments in healthy volunteers {{890 Liem-Moolenaar,M. 2010;}}. Schering-Plough report that they are investigating the effects of Org 25935 on negative symptoms, but no data have yet been released to the public domain. One concerning potential side effect of glycine transporter inhibitors is respiratory depression – although it is not clear if this affects all compounds in this class {{891 Perry,K.W. 2008;}}. Another issue is that the effect of GlyT1 inhibitors appears to occur only within a particular dose range, increasing NMDA receptor currents and long-term potentiation (LTP) within this range, but leading to reductions in NMDA receptor currents at higher doses {{892 Martina,M. 2004;}}.

Metabotropic glutamatergic receptors - allosteric potentiators

There has been some interest in developing allosteric potentiators of metabotropic glutamate receptors {{893 Johnson,M.P. 2004;}}, and two pharmaceutical companies have published data on these compounds (see Table 1). There are several theoretical advantages of allosteric potentiation in

targeting the glutamatergic system. As endogenous ligand is required for their action, they should have a lower propensity to side effects – they may also be less prone to desensitisation which occurs with drugs targeting the active site. LY379268 is an allosteric drug potentiating glutamate signalling at the mGlu2 receptor currently in development by Lilly. It has been shown to block ketamine induced glutamate release, as well as ketamine induced dopamine and histamine release in the prefrontal cortex, and norepinephrine release in hippocampus {{894 Fell,M.J. 2010;896 Lorrain,D.S. 2003;895 Lorrain,D.S. 2003;}}. It has also been shown to inhibit MK-801 induced retrosplenial cortex damage when injected into thalamus or cortex {{897 Carter,K. 2004;}}, suggesting that it may be neuroprotective in the early stages of psychosis.

3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) is an allosteric potentiator of the mGlu5 receptor developed by Merck {{898 Lindsley,C.W. 2004;}}. It increases the affinity of glutamate for the receptor, leading to an enhancement of NMDA receptor activity (figure 6). It has been shown to attenuate amphetamine-induced PPI deficits {{900 Kinney,G.G. 2005;}}, and to reverse MK-801 induced elevation in pyramidal cell activity {{899 Lecourtier,L. 2007;}}. It has also been shown to be effective in an animal model of negative symptoms (MK-801 induced impairment of sucrose-preference) {{902 Vardigan,J.D. 2010;}}, and has shown superior efficacy compared to mglu2/3 agonists in reversing MK-801 induced cognitive impairment {{903 Vales,K. 2010; 904 Stefani,M.R. 2010;}}. It shows a U-shaped dose-response curve on cognitive function and on GluR1 phosphorylation, however, suggesting a fairly tight therapeutic window {{901 Uslander,J.M. 2009;}}.

Glutamate and illness progression in schizophrenia – a critical window of opportunity?

Elevated cortical glutamate activity in schizophrenia appears to be most marked in the early phases of the illness {{643 Théberge, Jean 2002;}} and in the prodrome {{660 Stone, J.M. 2009;}}. Thus, it makes intuitive sense that drugs targeting excess glutamate release may be of most benefit when given during these stages. Indeed, as the illness progresses, it appears that, rather than being overactive, that cortical glutamate system may be reduced in function compared to healthy volunteers {{642 Théberge, Jean 2003;}}. It is tempting to speculate that administration of drugs that reduce cortical glutamate release (such as mGlu2/3 agonists), or inhibit its effects (such as AMPA antagonists and possibly minocycline) may be disease-modifying if given early enough - preventing transition to psychosis in individuals with prodromal symptoms and improving outcome in individuals with first-episode schizophrenia.

The evidence for a phase-specific deficit in NMDA receptor function is less clear, however. In one small SPECT study with the NMDA receptor ligand [123I]CNS-1261, unmedicated individuals with chronic schizophrenia were shown to have reduced NMDA receptor binding in left hippocampus {{188 Pilowsky}}. Thus, drugs targeting NMDA receptor enhancement (glycine_B agonists, GlyT1 antagonists and mGlu5 receptor agonists) may be of benefit at other phases of the illness including the prodrome and first-episode.

Clearly further work is required to investigate these hypotheses as studies to date have generally targeted individuals with chronic schizophrenia.

Conclusions

Novel drugs targeting glutamate transmission have shown considerable promise in the treatment of schizophrenia. Current evidence supports their use as adjunctive agents in individuals who fail to respond to conventional dopaminergic antipsychotic drugs, and preliminary data suggests that they are also efficacious as monotherapy. There are currently a large number of glutamatergic compounds in development, with a great deal of excitement about their potential as novel therapeutic agents in schizophrenia. It seems likely that the next wave of drugs for schizophrenia will target this system.

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Figure 1:

Glutamatergic synapse showing glutamate release, binding to AMPA and NMDA receptors on the postsynaptic membrane, and subsequent reuptake by astrocytes where it is metabolised to glutamine by glutamine synthetase (GS).

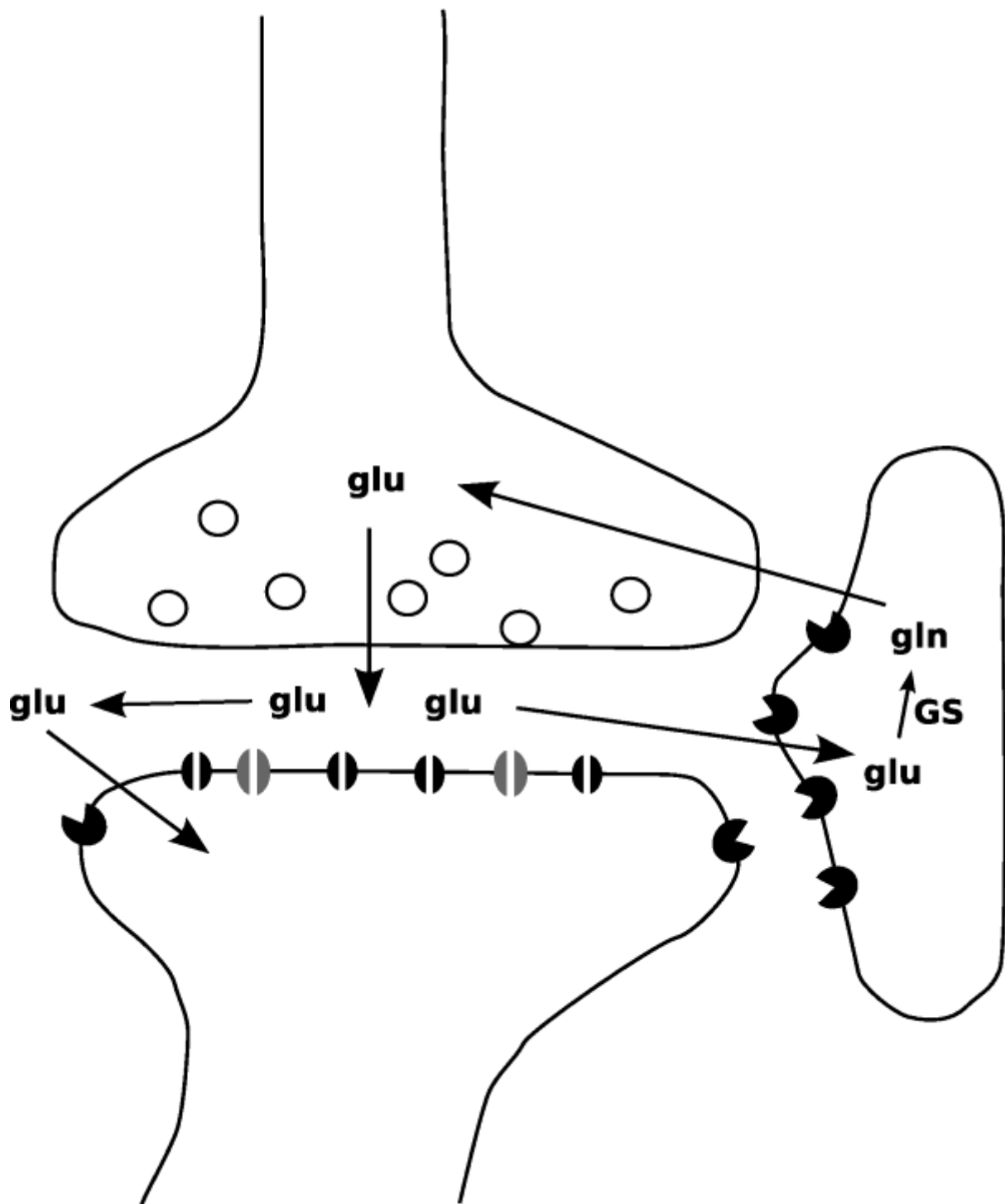


Figure 2:

Simplified diagram of an NMDA receptor with glycine (Gly), glutamate (Glu) and MK-801/PCP/ketamine (PCP) binding sites displayed. Extracellular calcium entry through the NMDA receptor occurs only when both glutamate and glycine bind to their respective binding sites, and the cell membrane depolarises allowing removal of the voltage-dependent block due to extracellular magnesium ions binding inside the pore of the NMDA receptor.

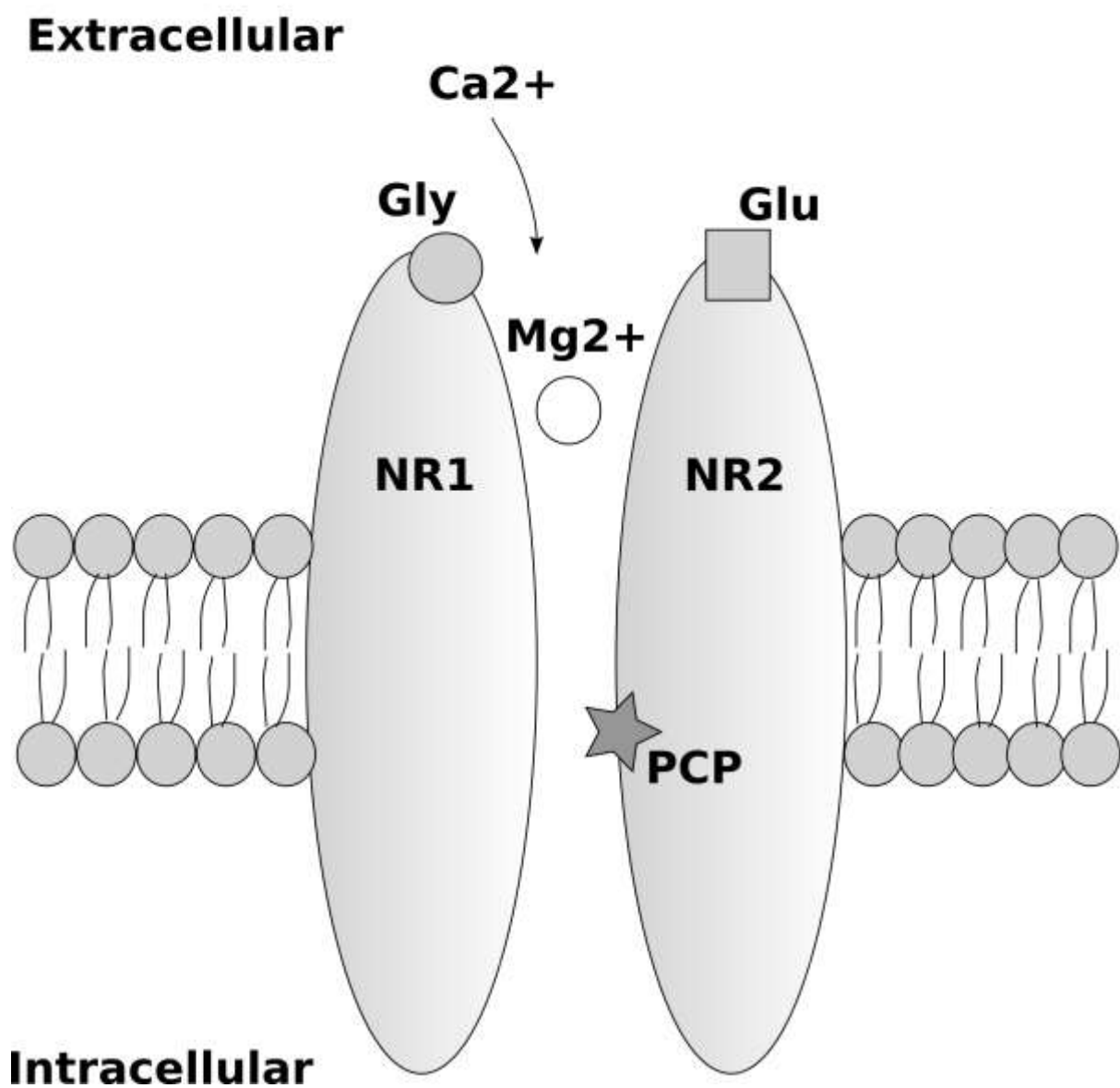


Figure 3:

Hypothesised mechanism whereby NMDA receptor antagonists lead to increased cortical glutamate release – inhibition of NMDA receptors expressed on GABAergic interneurons (A) leads disinhibition of glutamatergic projection neurons (B).

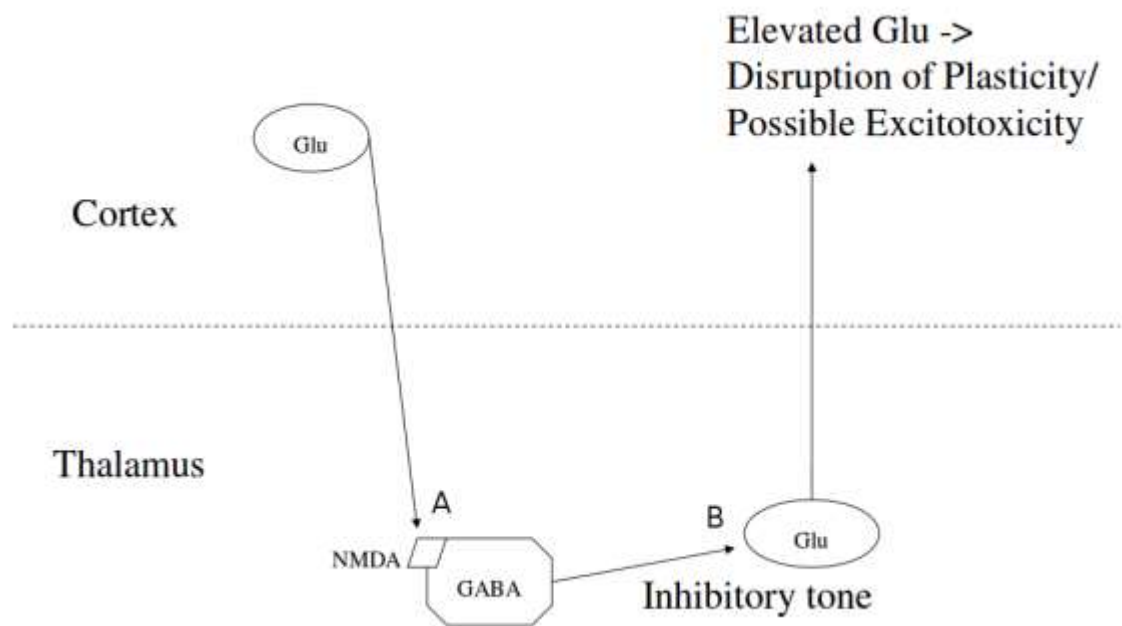


Figure 4:

Reduced NMDA receptor binding in left hippocampus in drug free patients with schizophrenia (DF) and matched healthy controls (HC) (see Pilowsky et al. 2006).

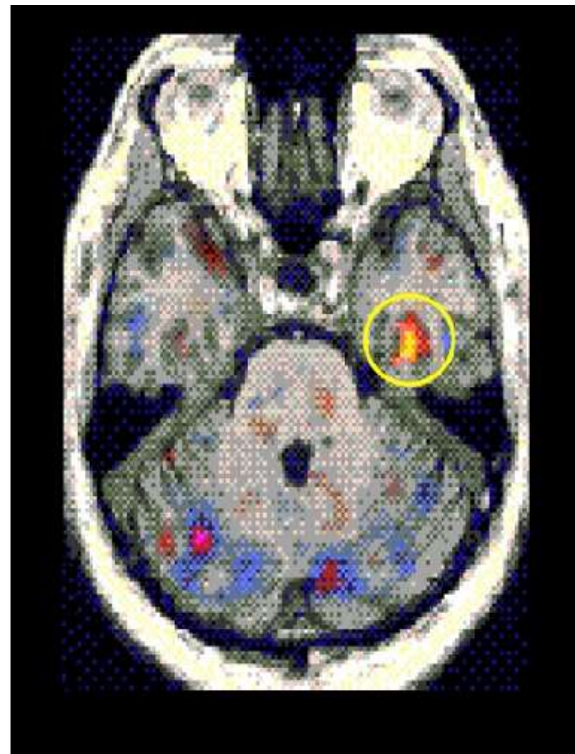
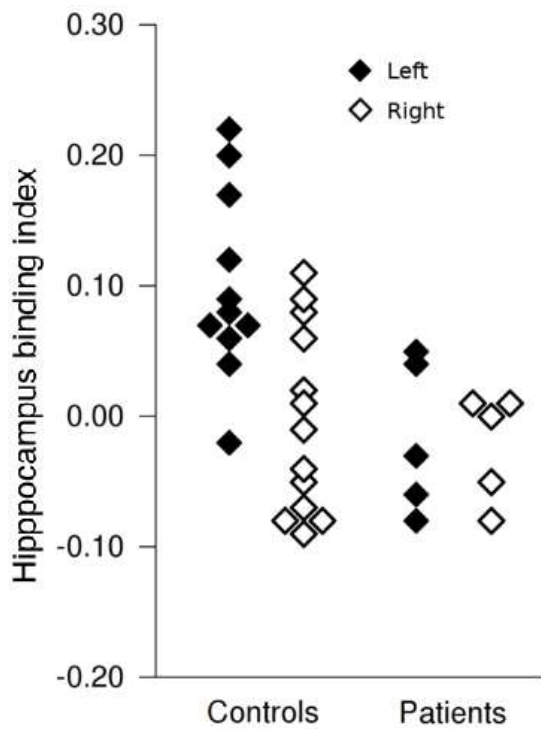


Figure 5:

Reduced NMDA receptor (NMDAR) expression on hippocampal GABA interneurons leads to increased sensitivity to reductions in presynaptic glutamate levels and disinhibition of glutamate efferents from hippocampus(A) leading to enhanced stimulation of GABA neurons projecting from nucleus accumbens (NAcc) to ventral pallidum (VP) resulting in enhanced inhibition of GABA neurons projecting from VP to ventral tegmental area (VTA) and disinhibition of dopamine (DA) neurons projecting to striatum (after Lodge et al. 2006).

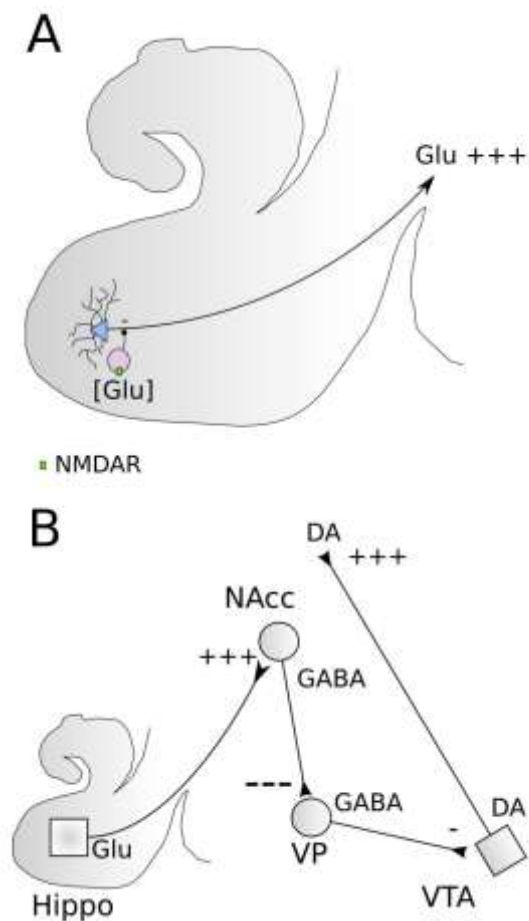


Figure 6:

Potential targets for drugs to reduce excess cortical glutamate release: Enhancement of NMDA receptor function by direct action at glycine_B site (2), or by increasing synaptic glycine concentrations through block of glycine transporters (1). Enhancement of NMDA receptor function through agonism of mGluR5 metabotropic glutamate receptors (3). Enhancement of GABA interneuron function through M1 or nicotinic alpha-7 agonism (4), or enhancement of BDNF function (5). Enhancement of GABA action on alpha-2 containing GABA-A receptors (6). Reduction of the effects of cortical glutamate release by blocking AMPA receptors (7), or by reducing glutamate release through mGlu2/3 autoreceptor agonism (8).

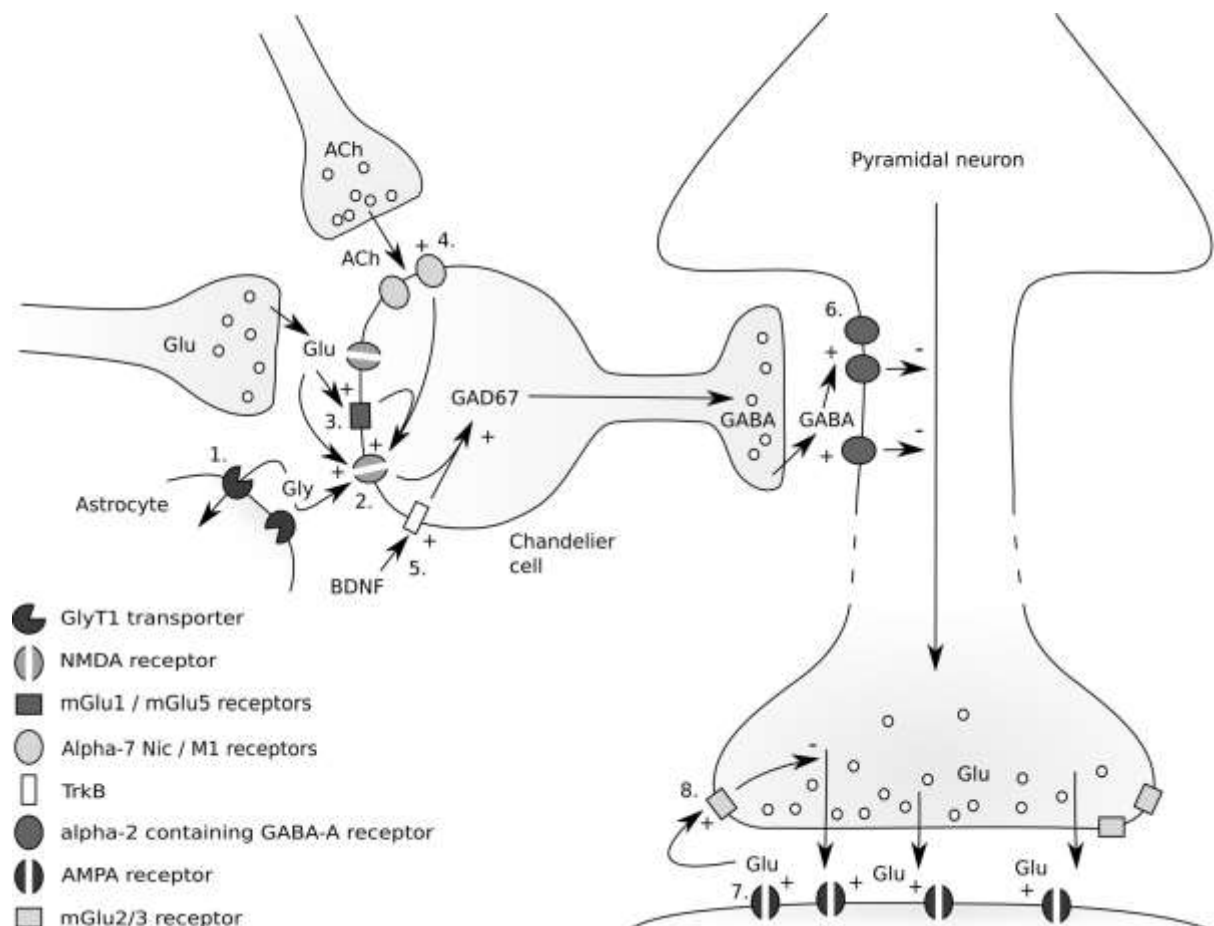


Table 1:

Glutamatergic drugs currently in development for the treatment of schizophrenia.

Company name	Drug name	Mechanism	Phase	Results
Roche	RG1678	GlyT1 inhibitor	Phase II	Effective vs. negative symptoms in patients with schizophrenia
Johnson & Johnson	R231857	GlyT1 inhibitor	Phase I	Improved scopolamine-induced cognitive impairments in healthy volunteers
Schering-Plough	Org 25935	GlyT1 inhibitor	?Phase II	No results in public domain
Lilly	LY379268	Allosteric mGlu2 potentiator	?	Preclinical effectiveness vs. ketamine and MK-801 models
Merck	CDPPB	Allosteric mGlu5 potentiator	?	Preclinical effectiveness vs. amphetamine, MK-801 and sucrose-preference (negative symptoms) models